

# Notice of Allowability

Application No.

09/373,403

Examiner

Anne L. Holleran

Applicant(s)

ARATHOON ET AL.

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to after-final filed 6/7/2007.
2. ☒ The allowed claim(s) is/are 56-77.
3. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
  - a) ☐ All    b) ☐ Some\*    c) ☐ None    of the:
  1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

\* Certified copies not received: \_\_\_\_\_.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.  
**THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.**

4. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.
5. ☒ CORRECTED DRAWINGS ( as "replacement sheets") must be submitted.
  - (a) ☒ including changes required by the Notice of Draftsperson's Patent Drawing Review ( PTO-948) attached
    - 1) ☐ hereto or 2) ☒ to Paper No./Mail Date 11/20/2002.
  - (b) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date \_\_\_\_\_.

Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).
6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

## Attachment(s)

- |  |  |
|--|--|
| 1. <input type="checkbox"/> Notice of References Cited (PTO-892)   | 5. <input type="checkbox"/> Notice of Informal Patent Application  |
| 2. <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                       | 6. <input checked="" type="checkbox"/> Interview Summary (PTO-413),<br>Paper No./Mail Date <u>20070802</u> . |
| 3. <input type="checkbox"/> Information Disclosure Statements (PTO/SB/08),<br>Paper No./Mail Date _____    | 7. <input checked="" type="checkbox"/> Examiner's Amendment/Comment  |
| 4. <input type="checkbox"/> Examiner's Comment Regarding Requirement for Deposit<br>of Biological Material | 8. <input checked="" type="checkbox"/> Examiner's Statement of Reasons for Allowance                         |
|  | 9. <input type="checkbox"/> Other _____  |

  
LARRY R. HELMS, PH.D.  
SUPERVISORY PATENT EXAMINER

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### EXAMINER'S AMENDMENT

An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in a telephone interview with Russell Boggs on 8/2/2007.

This application has been amended as follows:

In the claims:

Claims 30-36, 38, 40-43, 45-51, and 53-55 were canceled.

New claims 56-77 were added

Claim 56. A method of preparing a multispecific antibody comprising a first polypeptide and at least one additional polypeptide, the method comprising the steps of:

(i) culturing a host cell comprising a nucleic acid encoding a first polypeptide and a nucleic acid encoding at least one additional polypeptide, so that the nucleic acids are expressed; wherein

(a) the first polypeptide and each at least one additional polypeptide each comprise a heavy chain constant domain comprising a multimerization domain, and the multimerization domain of the first polypeptide forms an interface positioned to interact with an interface of the multimerization domain of the at least one additional polypeptide;

(b) the first polypeptide and each at least one additional polypeptide each further comprise a binding domain comprising a heavy chain variable domain and a light chain variable

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domain, wherein each binding domain binds to a different antigen and each light chain variable domain has the same amino acid sequence; and

(c) the multimerization domain of the first polypeptide interacts with the multimerization domain of the at least one additional polypeptide to form a multispecific antibody; and

(ii) recovering the multispecific antibody from the host cell culture.

Claim 57. The method of claim 56, wherein the multimerization domain of either the first polypeptide or the at least one additional polypeptide, or of both the first polypeptide and the at least one additional polypeptide, is altered by amino-acid substitution to form a non-naturally occurring disulfide bond between a free thiol-containing residue in the multimerization domain of the first polypeptide and a free thiol-containing residue in the multimerization domain of the at least one additional polypeptide.

Claim 58. The method of claim 56, wherein the interaction between the multimerization domain of the first polypeptide and the at least one additional polypeptide comprises a protuberance-into-cavity interaction.

Claim 59. The method of claim 58, wherein the protuberance is generated by altering the first polypeptide by substituting an amino acid of the first polypeptide with an amino acid that has a larger side chain volume than the substituted amino acid, and the cavity is generated by altering the at least one additional polypeptide by substituting an amino acid of the at least one additional polypeptide with an amino acid that has a smaller side chain volume than the substituted amino acid.

Claim 60. The method of claim 59, wherein the step of generating a protuberance or generating a cavity, or both, occurs by phage display selection.

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Claim 61. The method of claim 59 wherein the amino acid residue having a larger side chain volume than the substituted amino acid is selected from the group consisting of arginine (R), phenylalanine (F), tyrosine (Y), tryptophan (W), isoleucine (I) and leucine (L).

Claim 62. The method of claim 59, wherein the amino acid residue having a smaller side chain volume than the substituted amino acid is selected from the group consisting of glycine (G), alanine (A), serine (S), threonine (T), and valine (V), and wherein the amino acid residue having a smaller side chain volume than the substituted amino acid is not cysteine (C).

Claim 63. The method of claim 56, wherein the heavy chain constant domain is selected from the group consisting of a C<sub>H</sub>3 domain and a heavy chain constant domain of an IgG.

Claim 64. The method of claim 56 wherein step (i) is preceded by a step of introducing the nucleic acid encoding the first polypeptide and the at least one additional polypeptide into the host cell.

Claim 65. An isolated host cell comprising the nucleic acids encoding the multispecific antibody of claim 56.

Claim 66. The host cell of claim 65 wherein the host cell is a mammalian cell.

Claim 67. A method of preparing a multispecific antibody, the method comprising the steps of:

- (i) selecting a nucleic acid encoding a first polypeptide, a nucleic acid encoding a light chain, and at least one additional nucleic acid encoding at least one additional polypeptide;
- (ii) introducing into a host cell the nucleic acid encoding the first polypeptide, the nucleic acid encoding the light chain, and the at least one additional nucleic acid encoding the at least one additional polypeptide;
- (iii) culturing the cell so that the nucleic acid encoding the first polypeptide, the nucleic acid encoding the light chain, and the at least one additional nucleic acid encoding the at least one additional polypeptide are expressed, wherein

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(a) the first polypeptide and each at least one additional polypeptide each comprise a heavy chain constant domain comprising a multimerization domain and the multimerization domain of the first polypeptide forms an interface positioned to interact with an interface of the multimerization domain of the at least one additional polypeptide;

(b) the first polypeptide and each at least one additional polypeptide each further comprise a binding domain comprising a heavy chain variable domain and a light chain variable domain, wherein each binding domain binds to a different antigen and each light chain variable domain has the same amino acid sequence; and

(c) the multimerization domain of the first polypeptide interacts with the multimerization domain of the at least one additional polypeptide to form the multispecific antibody; and

(iv) recovering the multispecific antibody from the cell culture.

Claim 68. The method of claim 67, wherein the altering comprises generating a protuberance-into-cavity interaction at the interface between the first polypeptide and the at least one additional polypeptide.

Claim 69. The method of claim 67, wherein the altering comprises importing a free thiol-containing residue into the first polypeptide or the at least one additional polypeptide or both, such that the free thiol-containing residues interact to form a disulfide bond between the first polypeptide and the at least one additional polypeptide.

Claim 70. The method of claim 67 wherein the first polypeptide and the at least one additional polypeptide each comprise an antibody constant domain.

Claim 71. The method of claim 67 wherein the antibody constant domain is a C<sub>H</sub>3 domain.

Claim 72. The method of claim 67 wherein the antibody constant domain is the constant domain of a human IgG.

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Claim 73. A method of preparing a multispecific antibody comprising a first polypeptide and at least one additional polypeptide, the method comprising the steps of:

(i) culturing a host cell comprising a nucleic acid encoding a first polypeptide and a nucleic acid encoding at least one additional polypeptide, so that the nucleic acids are expressed; wherein

(a) the first polypeptide comprises a multimerization domain comprising a heavy chain constant domain forming an interface positioned to interact with an interface of a multimerization domain of the at least one additional polypeptide wherein said multimerization domain of the at least one additional polypeptide comprises a heavy chain constant domain,

(b) the first polypeptide and the at least one additional polypeptide each further comprise a binding domain, the binding domain comprising a heavy chain and a common light chain, wherein the common light chain of the first polypeptide and the at least one additional polypeptide has at least 98% sequence identity to a light chain of a first antibody and/or at least one additional antibody and only differs from each of the light chains of the first and/or the at least one additional antibody at amino acid positions outside of the CDR regions, and wherein the first and the at least one additional antibody bind to different antigens, and wherein each binding domain of the multispecific antibody binds to the different antigens; and

(ii) recovering the multispecific antibody from the host cell culture.

Claim 74. The method of claim 73, wherein the common light chain has 100% sequence identity to the light chain of a first antibody and the at least one additional antibody.

Claim 75. The method of claim 73, wherein each of the multimerization domains of the first polypeptide and the at least one additional polypeptide comprise a C<sub>H</sub>3 domain of an antibody constant domain.

Claim 76. The method of claim 75, wherein the multimerization domain of the first polypeptide has a protuberance and the multimerization domain of the at least one additional polypeptide has a cavity, wherein the protuberance and the cavity interact to form a protuberance-into-cavity interaction.

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Claim 77. The method of claim 76, wherein the multimerization domains further comprise a non-naturally occurring disulfide bond.

The following is an examiner's statement of reasons for allowance: The rejection of claims 30, 40, 41, 50 and 51 under 35 USC 102(b) as being anticipated by Nissim, as evidenced by Merchant is withdrawn. The provisional obviousness-type double patenting rejection over claims 47-63 of copending application no. 09/520,130 is withdrawn because the instant application has the same filing date as or an earlier filing date than copending application no. 09/520,130. The provisional obviousness-type double patenting rejection over claims 45-82 of copending application 10/143,437 (which has the same filing date as the instant application) is withdrawn because application 10/143,437 has issued as US Patent 7,183,076 with a terminal disclaimer listing the instant application.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne Holleran, whose telephone number is (571) 272-0833. The examiner can normally be reached on Monday through Friday from 9:30 am to 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, can be reached on (571) 272-0832. Any inquiry of a general nature or relating to the


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status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Official Fax number for Group 1600 is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

Anne L. Holleran  
Patent Examiner  
August 6, 2007



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